DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 1 2009

Rec'd 5/11/09

Michael Halstead
Associate General Counsel
Warner Chilcott
100 Enterprise Drive
Rockaway, N.J. 07866

Re: Docket No. FDA 2008-P-0586

Dear Mr. Halstead:

This responds to the citizen petition submitted on November 4, 2008 (Petition), to the Food and Drug Administration (FDA or the Agency) by Warner Chilcott (US), LLC (Warner Chilcott), and Mayne Pharma International Pty Ltd, the sponsor and manufacturer, respectively, of Doryx (doxycycline hyclate) Delayed-Release Tablets (Doryx DR Tablets). The petition requests that FDA ensure that any abbreviated new drug application (ANDA) referencing Doryx DR Tablets meet specified conditions for approval.

Specifically, the petition requests that FDA (1) not consider doxycycline hyclate tablets that contain an outer coating alone pharmaceutically equivalent to tablets with coated pellets, (2) only permit an ANDA to reference Doryx DR Tablets if FDA has granted a suitability petition, and (3) require ANDAs referencing Doryx DR Tablets to demonstrate comparability as follows:

- Bioequivalence to Doryx DR Tablets under all conditions specified in labeling, which includes sprinkling on applesauce, and administration under fed and fasting conditions.
- Same tablet image as Doryx DR Tablets (i.e., a scored tablet).
- Similar dissolution to Doryx DR Tablets, utilizing dissolution test methods cited in the proposed *United States Pharmacopeia* (USP) monograph entitled Doxycycline Hyclate Delayed Release Tablets, published in May-June 2008 (proposed USP monograph) (Petition at Attachment 9).

We have carefully reviewed the issues raised in your petition. For the reasons stated below, your petition is granted in part and denied in part.

FDA-2008-P-0586

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I. BACKGROUND

A. Doxycycline Hyclate

Doxycycline hyclate is a tetracycline-class antimicrobial used to treat infections caused by susceptible Gram-positive and Gram-negative organisms. Specifically, it is indicated for:

- Rickettsial infections
- Sexually transmitted infections
- Respiratory tract infections
- Specific bacterial infections
- Anthrax, including inhalational anthrax
- Alternative treatment for selected infections when penicillin is contraindicated
- Adjunctive therapy in acute intestinal amebiasis
- Severe acne
- Prophylaxis of malaria

Doxycycline hyclate was initially approved in 1967 and has been approved in a variety of different dosage forms, including delayed-release and immediate-release oral tablets and capsules.

Doryx DR Tablets contain coated pellets of doxycycline hyclate. The delayed-release coating does not surround the outer tablet, but instead surrounds the doxycycline hyclate pellets which are compressed to form the tablet.. FDA approved the 75-milligram (mg) and 100-mg strengths of Doryx DR Tablets on May 6, 2005 (new drug application (NDA) 50-795).[1] Doryx (doxycycline hyclate) Delayed-Release Capsules (Doryx DR Capsules), also containing coated pellets, were approved in 1985, but subsequently discontinued from sale.[2]

B. Statutory and Regulatory History

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD)[3] is safe and

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[1] FDA approved the 150-mg strength scored tablet on June 6, 2008, the 100-mg strength scored tablet on February 11, 2009, and the 75-mg strength scored tablet on March 6, 2009.

[2] Warner Chilcott submitted a citizen petition on September 10, 2004 (Docket No. 2004P-0417), requesting that FDA ensure that any ANDA referencing Doryx DR Capsules meet specified conditions for approval similar to those requested in this petition. After it discontinued marketing Doryx DR Capsules, on June 14, 2006, Warner Chilcott withdrew its petition concerning Doryx DR Capsules.

[3] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs

effective. A drug product described in an ANDA generally must contain the same active ingredient,[4] conditions of use,[5] route of administration, dosage form, strength,[6] and (with certain permissible differences) labeling[7] as the RLD, unless a petition for certain changes is approved by the Secretary (section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the Act). An applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a petition to the Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency's approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).

Under the Hatch-Waxman Amendments, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic drug[8] is bioequivalent to the RLD.[9] Section 505(j)(8)(B)(i) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if:

> ... the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses...[10]

FDA's regulations in 21 CFR part 320 list acceptable methodologies for determining the bioequivalence of drug products.[11] These methodologies include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies. The choice of which study design to use is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug. The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence

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are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).

[4] See, e.g., 21 CFR 314.94(a)(5).

[5] See, e.g., 21 CFR 314.94(a)(4).

[6] See, e.g., 21 CFR 314.94(a)(6).

[7] See, e.g., 21 CFR 314.94(a)(8).

[8] For purposes of this response, the term *generic drug* refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[9] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) [i.e., listed drug]..."); 21 CFR 314.3 (defining *reference listed drug*); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug upon which the applicant relies); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA); and the Orange Book, Introduction at x (defining *reference listed drug*).

[10] See also 21 CFR 320.1(e) and 320.23(b).

[11] Although you cite 21 CFR 320.33 as relevant to your petition (Petition at 2), we note that this section of our regulations enumerates criteria to be used in evaluating whether products previously believed to be pharmaceutical equivalents and pharmaceutical alternatives present actual or potential bioequivalence problems. You have not, however, provided any evidence that a potential generic product is not bioequivalent to Doryx DR Tablets. As articulated in this response, we expect to approve only generic versions of doxycycline hyclate delayed-release tablets that are bioequivalent to Doryx DR Tablets.

requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

For in vivo pharmacokinetic tests, FDA generally considers two products to be bioequivalent when the 90 percent confidence intervals for the ratios of the pharmacokinetic parameters (area under the plasma concentration vs. time curve (AUC) and maximum drug concentration (C_{max})) are entirely within an 80 to 125 percent acceptance interval. The use of an 80 to 125 percent acceptance interval is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients.[12]

Food administered with a drug product may change bioavailability by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the bioavailability of a drug product without conducting specific mechanistic studies. The Agency has issued guidance to provide recommendations to sponsors and/or applicants of immediate-release and modified-release drug products planning to conduct food-effect bioavailability and fed bioequivalence studies for orally administered drug products (see FDA guidance for industry entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies* (the food-effect guidance)).[13] The food-effect guidance also provides information on when food-effect bioavailability and fed bioequivalence studies should be performed, and addresses how to meet the bioavailability and bioequivalence requirements in part 320 and §§ 314.50(d)(3) (21 CFR 314.50(d)(3)) and 314.94(a)(7) as they apply to oral dosage forms.

Drug products that meet the approval requirements under section 505(j) of the Act and are both bioequivalent and pharmaceutically equivalent[14] to the RLD are considered by FDA to be therapeutically equivalent to the RLD. Therapeutically equivalent drugs generally may be substituted for each other with the expectation that the substituted product will produce the same clinical effect and safety profile when used according to the labeling.[15] The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the following criteria are therapeutically equivalent and may be substituted for each other: (1) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; (2) meet applicable standards of strength, quality, purity and identity; (3) are manufactured in compliance with current good manufacturing practice regulations; and (4) are adequately labeled.

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[12] See FDA guidance for industry entitled *Statistical Approaches to Establishing Bioequivalence* (available on the Internet at http://www.fda.gov/cder/guidance/index.htm); the Orange Book, 29th Ed., Introduction at pp. ix-x.

[13] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[14] Pharmaceutically equivalent drug products have the same dosage form and contain the same amounts of the same active drug ingredient and meet the same compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling (see 21 CFR 320.1 and the Orange Book, Introduction at pp. vi-vii).

[15] See the Orange Book, Introduction at p. vii.

II. DISCUSSION

A. Dosage Form and Pharmaceutical Equivalence

You request that FDA confirm that tablets containing doxycycline hyclate with an outer coating alone should not be considered pharmaceutically equivalent to tablets with coated doxycycline hyclate pellets (Petition at 1). You claim that tablets that contain an outer coating alone are not the same dosage form as tablets that contain coated pellets, and therefore are not pharmaceutically equivalent to Doryx DR Tablets (Petition at 1-2).

As noted in section I.B of this response, the Act requires a generic drug product to have the same dosage form as the RLD (21 U.S.C. 355(j)(2)(A)(iii)). In addition, as you correctly state, for two products to be considered AB-rated — that is, therapeutic equivalents and thus substitutable — they must be both bioequivalent and pharmaceutically equivalent (Petition at 4). Under our current thinking, tablets that contain an outer coating alone are not automatically classified as a different dosage form from tablets that contain coated pellets. The term *dosage form* is not separately defined in the Act or in FDA's regulations. The term, however, is used in the definition of a *drug product*, which is defined as "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance . . ." (21 CFR 314.3(b)). As this definition illustrates, a dosage form is the way of identifying the drug by its physical form, which is linked both to the physical appearance of the drug product and to the way it is administered.[16] See also *Pfizer Inc. v. Shalala*, 1 F. Supp. 2d 38, 46 aff'd in part and rev'd in part, 182 F. 3d 975 (D.C. Cir. 1999) ("a drug's dosage form is not based on its release mechanism but on its appearance and the way the drug was administered").

As you note, the dosage form listed in the *Approved Drug Products With Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book, for Doryx DR Tablets is "Tablet, Delayed Release" (Petition at 5). FDA has published a list of dosage forms in Appendix C of the Orange Book. Although this list is not binding, it provides guidance for industry on what constitutes the "same" or "identical" dosage form. In general, the "same dosage form" requirement is met if the dosage form of the proposed generic drug product falls within the same dosage form category in the Orange Book as the RLD. We agree that for a generic doxycycline hyclate delayed-release tablet to be considered pharmaceutically equivalent to Doryx DR Tablets, it must be a delayed-release tablet, consistent with the category "Tablet, Delayed Release" in Appendix C of the Orange Book.

As you note in your petition (at 4-5), pharmaceutical equivalents may differ in characteristics such as shape, scoring, release mechanism, and, within certain limits,

[16] As noted above, the Act requires a generic drug product to have the same dosage form as the RLD (21 U.S.C. 355(j)(2)(A)(iii)). Approved generic drug products that have the same dosage form as the RLD, among other characteristics, are "pharmaceutical equivalents" (21 CFR 320.1(c)) and may be rated therapeutically equivalent in the Orange Book.

labeling (see Orange Book at vii). A review of the dosage form classifications in the Orange Book demonstrates that the Agency has consistently chosen not to base its dosage form descriptions on release mechanisms.[17] In the regulation detailing reasons to refuse to approve an application, the Agency implicitly acknowledges that the "release mechanism" is a part of the composition or formulation of the drug rather than the "dosage form" of the drug (see 21 CFR 314.127(a)(8)(ii)(A) ("FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application . . . Examples of changes that may raise serious questions of safety or efficacy include, but are not limited to, the following: . . . The use of a delivery or a modified release mechanism never before approved for the drug.")).[18]

Once it is established that the enteric coated tablets and tablets containing coated pellets can be the same dosage form, it follows that enteric coated tablets and tablets containing coated pellets can be pharmaceutical equivalents. FDA regulations recognize that extended-release products that deliver the identical amounts of the active ingredient over the same dosing period can be pharmaceutical equivalents (see section I.B, including footnote 14, of this response). FDA has considered numerous products with different release mechanisms to be pharmaceutically equivalent.[19] Furthermore, as FDA has noted previously, there is "no scientific basis for distinguishing dosage forms on the basis of release mechanisms." Moreover, "bioequivalency standards assure the therapeutic equivalence of any pharmaceutically equivalent extended-release product."[20]

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[17] The release mechanism is not specifically considered in evaluating whether two drug products have the same dosage form; however, the Agency could refuse to approve an ANDA if it found that a difference in release mechanism caused the composition of the proposed drug product to be unsafe (21 CFR 314.127(a)(8)(i)(B)), or if it caused the proposed drug product to not be bioequivalent to the reference listed drug.

[18] See also Preamble to Final Rule Implementing Hatch-Waxman Amendments, (57 FR 17950, 17969, April 28, 1992) (equating change in release mechanism with other changes in inactive ingredients, not changes in dosage form).

[19] Examples of FDA approved drug products with different release mechanisms that FDA has found to be therapeutically equivalent (pharmaceutically equivalent and bioequivalent) include:
(a) ANDA 75-269, Nifedipine Extended-Release Tablets, Biovail Laboratories Inc., which has an extended-release coating, was designated therapeutically equivalent to NDA 19-684, Procardia XL (Nifedipine) Extended-Release Tablets, Pfizer Inc., which has an osmotic extended-release mechanism.
(b) ANDA 76-467, Glipizide Extended-Release Tablets, Watson Laboratories, which has an extended-release coating, was designated therapeutically equivalent to NDA 20-329, Glucotrol XL (Glipizide) Extended-Release Tablets, Pfizer Inc., which has an osmotic extended-release mechanism.
(c) NDA 20-704, Claritin Reditabs (Loratidine Orally Disintegrating Tablets), Schering Plough Corp., over-the-counter drug product utilizing a certain orally disintegrating tablet technology was designated therapeutically equivalent to multiple ANDAs that use different orally disintegrating tablet technology. See also *Pfizer Inc., v. Shalala*, 1 F. Supp. 2d 38, (D.D.C. 1998); 182 F.3d 975 (D.C. Cir. 1999) (regarding nifedipine); *Warner-Lambert Co. v. Shalala*, 202 F.3d 326 (D.C. Cir. 2000) (regarding phenytoin). In both cases, the court upheld FDA's approval of an ANDA product where the generic capsule/tablet version was considered the same dosage form as the RLD's capsule version.

[20] FDA Response to Citizen Petition by Pfizer, Inc., Docket No. 93P-0421 at 5,11 (August 12, 1997); FDA Consolidated Response to four citizen petitions: ALZA Corp, Docket No. 2004P-0506, Daniel Brookoff, Docket No. 2004P-0472, Christopher Mead, Docket No. 2004P-0540, and Steven Shafer, 2004P-0340, at 4-5 (January 28, 2005).

Doxycycline hyclate is known to cause gastrointestinal irritation. To support your argument that Doryx DR Tablets are a unique dosage form distinguishable from tablets with an outer coating alone, you claim that the pH-dependent pellet coating offers clinical advantages over powder-filled capsules or immediate-release oral tablets because they significantly reduce the risk of gastrointestinal irritation or stomach upset (Petition at 2, 3). To support this claim, you provide three literature articles (Petition at Attachments 2, 3, 4). Each article presents a study comparing the incidence of gastrointestinal complaints when comparing doxycycline DR capsules (claimed to be functionally identical to Doryx DR Tablets) with an immediate-release doxycycline hyclate powder-filled capsule formulation and with a placebo. You claim that in each study, the healthy subjects who received the doxycycline DR capsule formulation reported statistically significant fewer incidences of nausea or abdominal discomfort than those who received the immediate-release formulation. Regardless of the formulation, subjects who received placebo experienced fewer incidences of nausea or abdominal discomfort than those who received doxycycline hyclate.

We do not agree that the studies you submitted are sufficient to support a claim that Doryx DR Tablets significantly reduce the risk of gastrointestinal irritation or stomach upset. We have found design flaws with each of these studies. For example, we note that all these studies were conducted in healthy volunteers rather than patients and this may affect gastrointestinal adverse events. One study compared the incidence of nausea after administration of only a single dose of drug, but the value of this information is limited because patients generally receive a multi-day course of the drug product and rates of nausea may change with repeated dosing. Another article did not adequately explain the clinical meaning of the scoring system for symptoms or how the diaries and symptom scoring were validated. The results from these studies suggest that doxycycline DR capsules cause more gastrointestinal events compared to placebo. These results are consistent with the labeling for Doryx DR Tablets, which contains the same information about gastrointestinal adverse reactions as other doxycycline hyclate formulations. The relevant language in the *Adverse Reactions* section (6.1) of labeling for Doryx DR Tablets prominently lists "nausea" and "vomiting" as adverse reactions but does not quantify the frequency of these events. Although the Doryx DR Tablets may be designed to minimize adverse reactions by maintaining the tablets' delayed-release properties when the tablet is broken or the outer surface is otherwise disrupted, the labeling for Doryx DR Tablets and the additional information referenced in the petition do not, at this time, support a claim of clinical advantage over other doxycycline hyclate formulations.

Thus, FDA denies your request to confirm that tablets containing doxycycline hyclate with an outer coating alone are, by definition, a different dosage form and therefore not pharmaceutically equivalent to Doryx DR Tablets. However, the statutory and regulatory requirements discussed in section 1.B, including the standards for therapeutic equivalence and bioequivalence (see footnote 14), are applicable to ANDAs for delayed-release products. If it is determined that the safety or efficacy of a specific drug product proposed for approval in an ANDA is affected because it has an outer coating rather than coated pellets, that ANDA would not be approved. To the extent appropriate, FDA will apply these requirements to ANDAs referencing Doryx DR Tablets.

B. Applicable Compendial Standards and Dissolution Methodologies and Specifications

You request that FDA require any ANDA referencing Doryx DR Tablets to demonstrate acceptable dissolution by using the dissolution test methods cited in the proposed USP monograph for doxycycline hyclate delayed-release tablets (Petition at 1, referring to Attachment 9). You request that FDA require any such ANDA meet the applicable standards for strength, quality, purity, and identity contained in the proposed USP monograph, and you note that USP provides different standards for other formulations, including one for "Doxycycline Hyclate Tablets," applicable to immediate-release doxycycline hyclate tablets (Petition at 5, referring to Attachment 8). You explain the dissolution test is different in the doxycycline hyclate tablet monograph and the doxycycline hyclate delayed-release tablet proposed monograph and that any ANDA product that references Doryx DR Tablets should meet the proposed dissolution test standards (i.e., using acid and buffer mediums) in the proposed delayed-release tablet monograph, even when the tablet is broken in half (Petition at 6). You argue that any ANDA that fails to meet the proposed compendial standards would not be pharmaceutically equivalent to Doryx DR Tablets (Petition at 5).

Under section 501(b) of the Act (21 U.S.C. 351(b)), a drug is adulterated if "it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium." To be considered pharmaceutically equivalent to Doryx DR Tablets, a doxycycline hyclate delayed-release tablet must demonstrate that it contains identical amounts of the identical active drug ingredient and meets "the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates" (21 CFR 320.1(c)).

FDA is aware that doxycycline hyclate immediate-release and delayed-release tablet formulations have different release characteristics and that they have different dissolution specifications reflective of their respective release rates and mechanisms. FDA is also aware that USP has different monographs and proposed monographs for the immediate-release and delayed-release doxycycline hyclate formulations. Therefore, FDA would not expect delayed-release tablets to meet the compendial standards applicable to immediate-release tablets. For drug products with official, final USP monographs, ANDA applicants are expected to comply with all monograph standards.[21]

Specifically, you state that the drug release method provided in the proposed USP monograph requires that the contents of the doxycycline hyclate tablet be evaluated in

[21] However, if the in vitro dissolution method and/or specification in the official, final USP monograph is/are not appropriate for a newly approved generic product (because the generic product contains different inactive ingredients from the RLD), the generic product may temporarily be labeled as a USP product with a statement such as, "USP dissolution method pending." The ANDA holder would then petition USP to incorporate its FDA-recommended method and/or specification into the existing monograph.

both an acid and a buffer medium to determine the amount of doxycycline dissolved at each stage (Petition at 6). You further state that the tolerances provided for each stage of dissolution testing require that in the acid stage, not more than 30 percent of the labeled amount be dissolved in 20 minutes and that in the buffer stage, not less than 85 percent of the labeled amount of doxycycline be dissolved in 30 minutes (Id.). You note, however, that the proposed USP monograph for delayed-release doxycycline hyclate formulations is not yet a final monograph.

Although the proposed doxycycline delayed-release tablet monograph is not yet final, FDA would expect dissolution testing of any delayed-release dosage form to comply with the general procedures for delayed-release dosage forms described in Chapter <711> USP 31 (2008). According to that chapter, for delayed-release tablets, comparative dissolution should be studied in acid and buffer media for the whole units (in addition to half units if the reference listed tablet is scored) to ensure that (1) the enteric coating is acid resistant (acid phase testing), and (2) stability and production batches meet stability and quality control standards (both acid and buffer phase testing). FDA would expect any ANDA applicant referencing Doryx DR Tablets to show acceptable dissolution in an acid and a buffer and either meet the specifications proposed for doxycycline hyclate delayed-release tablets in the proposed monograph or use an alternative method that the Agency finds acceptable (see footnote 21).

You further request that FDA require any ANDAs for delayed-release doxycycline hyclate referencing Doryx DR Tablets to have the same tablet image as Doryx DR Tablets (i.e., a scored tablet) (Petition at 1). A scored tablet is intended to be broken in half, each half supported by dose equivalence testing, with each half maintaining its delayed-release properties. We note that all strengths of Doryx DR Tablets are now scored (see footnote 1). As you describe in the petition (at 6-7), three labeled prescribing conditions necessitate breaking the tablets: (1) the optional maintenance dose of 50 mg that can be obtained only by breaking the 100-mg strength tablet in half, (2) the varied body weight-based pediatric doses that may include administration of strengths less than 75 mg, and (3) the dosing of broken tablets sprinkled on applesauce.

For scored dosage strengths of a tablet formulation where the labeled conditions of use require that the tablet be broken, FDA typically requires that corresponding generic versions also be scored.[22] FDA requires evidence of content uniformity for any scored tablet. In addition to demonstrating acceptable content uniformity, ANDA applicants must also ensure that each half maintain a similar release profile to that of the whole tablet (generally by conducting whole- and half-tablet dissolution testing). These tests provide information on the performance of the dosage form once broken, which allows FDA to assess content distribution of the active pharmaceutical ingredient in the generic product under the conditions of use described in labeling.

[22] See Center for Drug Evaluation and Research's Manual of Policies and Procedures (MAPP) 5223.2, *Scoring of Configuration of Generic Drug Products*, available on the Internet at http://www.fda.gov/cder/mapp.htm.

Therefore, although a generic product may not be required to comply with the proposed compendial standards for doxycycline hyclate delayed-release tablets per se because that USP monograph is not yet final, it is expected to comply with the general USP monograph for delayed-release tablets and to show acceptable content uniformity and acceptable dissolution, including when the tablet is broken in half. Thus, your request is granted in part.

C. Bioequivalence

You request that FDA require that all ANDA applicants referencing Doryx DR Tablets conduct bioequivalence studies under all dosing conditions specified in labeling, including sprinkling on applesauce, administering with food, and administering under fasting conditions (Petition at 1 and 7). You state that any ANDA referencing Doryx DR Tablets must meet the bioequivalence requirements cited in 21 CFR 320.23 and 320.24 (Petition at 7). Specifically, you state that the bioequivalence of the test to the reference drug should be demonstrated in a single-dose crossover study in which both treatments are sprinkled on one of the soft foods mentioned in the labeling (i.e., applesauce), and that the 90 percent confidence interval criteria should be used to declare bioequivalence (Id.).

FDA agrees that ANDA applicants must demonstrate bioequivalence under the dosing conditions described in the labeling. As stated in section II.A of this response, for two products to be considered AB-rated therapeutic equivalents, they must be both pharmaceutical equivalents and bioequivalent under approved conditions of use.

As described in section I.B of this response, our food-effect guidance explains when food-effect bioequivalence studies should be conducted for modified-release drug products. Because Doryx DR Tablets are labeled for administration under fed and fasted conditions, any ANDA referencing Doryx DR Tablets should demonstrate bioequivalence under both fed and fasted conditions. Because sprinkling on applesauce is also a condition of use described in the labeling for Doryx DR Tablets, any ANDA applicant would need to demonstrate bioequivalence when the tablet is broken and sprinkled on applesauce. Consistent with the guidance recommendations for modified-release drug products, any ANDA referencing Doryx DR Tablets should demonstrate bioequivalence under the approved conditions of use by demonstrating (1) bioequivalence under fasting conditions, (2) bioequivalence under fed conditions, and (3) bioequivalence when the contents of the tablet are sprinkled on applesauce.

As discussed previously and described in the food-effect guidance, FDA assures that the 90 percent confidence intervals of the geometric test/reference ratios of the AUC and the C_{max} parameters are within the 80 to 125 percent bioequivalence limits. In addition, FDA carefully reviews the T_{max} parameter of test and reference means, which is a measure of time to maximum plasma concentration of doxycycline hyclate.

Therefore, your request that applicants demonstrate bioequivalence under fed and fasted conditions and when sprinkled on applesauce is granted.

D. Suitability Petition

You request that FDA only permit an ANDA to use Doryx DR Tablets as the reference listed drug if FDA has granted a suitability petition (Petition at 1).

As explained in section I.B of this response, an applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a suitability petition to the Agency requesting permission to file such an application and has received the Agency's approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93). We assume that you have requested that FDA require generic applicants to submit a suitability petition based on your belief that a doxycycline hyclate tablet with an outer coating alone would be a different dosage form from Doryx DR Tablets (Petition at 1-2). As discussed in section II.A, we disagree that an ANDA for a doxycycline hyclate delayed-release tablet that contains coated pellets is a different dosage form from a doxycycline hyclate delayed-release tablet that uses a different release mechanism. Therefore, we disagree that an ANDA for a doxycycline hyclate delayed-release tablet would be required to submit a suitability petition before submitting an ANDA referencing Doryx DR Tablets.

Were an ANDA applicant to seek to submit an application referencing Doryx DR Tablets for a doxycycline hyclate product that was considered a different dosage form, then submission of a suitability petition under § 314.93 would be an appropriate regulatory option. Otherwise, unless the applicant is seeking approval for a change of the type enumerated under § 314.93, submission of a suitability petition is unnecessary.

Therefore, your request is denied.

III. CONCLUSION

For the reasons described above, your petition has been granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research